REMARKS/ARGUMENTS

Reexamination and reconsideration of this Application, withdrawal of the rejections, and formal notification of the allowability of all claims as now presented are earnestly solicited in light of the above claim amendments and remarks that follow.

Claim 27 has been amended to remove the word "substantially." Claims 43-45 have been amended to remove the phrase "a therapeutically effective amount of." Claim 44 has been amended to remove the word "permeated." Claims 50 and 51 have been amended to correct the dependency thereof. Claims 27-37, 41, and 43-51 are pending.

Claim Objections

Claim 50 is objected to as being a substantial duplicate of claim 48. Claim 51 is objected to as being a substantial duplicate of claim 49. As noted above, claims 50 and 51 have been amended to correct the dependency thereof. These claims now depend from claim 45 instead of claim 44. Applicant respectfully submits said amendment overcomes the objection.

Rejections under 35 U.S.C. §112

Claims 27-37, 41, and 43-51 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicant respectfully traverses this rejection.

Claims 43-45 (and dependant claims 27-37, 41, 47, 49, and 51) are rejected for use of the term "recombinant." The examiner argues the term is indefinite because the specification discloses a definition that allegedly makes the claims unclear.

Applicant respectfully submits that the examiner is going to undue lengths to complicate prosecution of the present application. According to MPEP 2173.02, the examiner's focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C. 112, second paragraph, is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available. The claims only must define the patentable subject matter with a reasonable degree of particularity and distinctness. Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire. Regarding the term "recombinant," the examiner is reminded of the ruling in *Raytheon Co. v. Roper Corp.*, 724 F.2d

951, 957 (Fed. Cir. 1983), where the court noted "[t]hat claims are interpreted in light of the specification does not mean that everything in the specification must be read into the claims." The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of: (A) the content of the particular application disclosure; (B) the teachings of the prior art; and (C) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

The specification provides a definition of the term recombinant that clearly and unambiguously provides the public with a reasonable degree of clarity and particularity of what is being claimed – i.e., any type of cloned therapeutic expressed in prokaryotic cells or a genetically engineered molecule. That the examiner is unfamiliar with the field of combinatorial libraries of molecules does not make the claim term indefinite. Under the test described above, (A) the present disclosure provides a clear and unambiguous definition of the term that would be understood by the skilled person, (B) the prior art is replete with teaching around recombinant molecules, and (C) a skilled person would clearly be able to understand what is being claimed by use of the term recombinant, regardless of the definition provided in the specification. Applicant has in fact gone beyond what is required to make the claim term definite, and under the ruling in *Raytheon Co. v. Roper Corp.*, it is improper for the examiner to reject the claim because the examiner is unfamiliar with one definition provided in the specification when there is a further definition in the specification that the examiner has not objected to. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the present rejection.

Claims 43-45 are rejected for use of the term "therapeutically effective amount." The claims have been amended to remove this term. Thus, Applicant requests reconsideration and withdrawal of this rejection.

Claim 27 is rejected for use of the term "substantially." The claim has been amended to remove this word. Thus, Applicant requests reconsideration and withdrawal of this rejection.

Claim 44 is rejected for use of the phrase "permeated in the pores." The claim has been amended to remove the word "permeated." Thus, Applicant requests reconsideration and withdrawal of this rejection.

Rejection under 35 U.S.C. §102

Claims 27-29, 35, 41, 43-45, 47, 49, and 51 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Schröder (Methods in Enzymology, 1985). Applicant respectfully traverses this rejection.

In continuing to rely upon Schröder, the examiner clings to the argument that Schröder discloses dextran and insulin. The examiner disregards all other arguments because, in the examiner's reasoning, if Schröder discloses dextran and insulin, the composition of the present invention must be the same. This logic is not supported by prevailing law.

First, the examiner points to page 123, row 1, of Schröder. The examiner, however, ignores the footnote at the bottom of the table, which states that the insulin was entrapped in the dextran. The present claims recite not just a composition of dextran and insulin, but the claims recite a specific type of combination of the materials that is different and unobvious from the specific type of combination described by Schröder. Applicant does not suggest that the simple combination of dextran and insulin is new. Applicant does submit that the art has not heretofore disclosed or suggested combining insulin and dextran in the manner presently claimed, which imparts to the composition particular properties that make the form of the combination new and nonobvious.

First and foremost, Schröder unambiguously teaches that the insulin in its composition is **entrapped** in the dextran. Present claim 43 recites that none of the insulin is encapsulated by the porous crystallized dextran microparticles. To get around this claim language, the examiner takes a torturous interpretation of the present specification. In parsing the language from the specification, the examiner sidesteps the obligation to give the claims their broadest possible interpretation. Moreover, the examiner overlooks the fact that claims must be given an interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. A skilled person would understand what is meant by the term "encapsulation" and would not attempt to limit the claim scope in the same manner as the examiner has now done.

The examiner argues that paragraph [0073] describes encapsulation as acting as a shell, and the examiner argues that the Schröder composition does not act like a shell. The examiner

fails to recognize, however, that paragraph [0083] contrasts the present invention from prior art methods wherein the therapeutic agent is encapsulated into a microparticle shell by providing the particle precursor material and the therapeutic agent into a solution and then crystallizing or cross-linking the precursor material, such as a monomer or oligomer material, to encapsulate a therapeutic agent core into a microparticle shell. This is the exact method employed by Schröder to encapsulate its insulin. At page 120 (under the heading "Crystallized Carbohydrate Spheres (CCS) for Slow Release"), Schröder discloses that his composition relates totally to **entrapment** of substances for slow release. The text thereafter discloses that the dextran and the active substance "to be entrapped" are co-dissolved and then precipitated to form spheres wherein the active substance is entrapped therein. Thus, it is clear that the Schröder composition relies exactly upon the type of entrapment or encapsulation that the presently claimed invention distinguishes and overcomes.

At page 14 of the office action, the examiner argues that the instant claims to not exclude entrapment. This is wrong. Claim 43 recites that none of the insulin is encapsulated by the porous crystallized dextran microparticles. Moreover, claim 45 recites that the insulin is only in the microparticles by being located in pores of the microparticles.

At page 15 of the office action, the examiner again argues that the present specification limits the claims to excluding cases where an encapsulating material acts like a shell from which there is no escape. Initially, this is an absurd allegation because there **is** an escape from a shell – the shell is merely broken (e.g., degraded or dissolved). One of skill in the art would readily recognize that encapsulating materials can be degraded by various means to release the components encapsulated therein. In fact, U.S. Pat. No. 4,713,249 (upon which the examiner also relies) actually makes Applicant's point. The '249 patent by Schröder teaches at column 2 (lines 61-64) that the biologically active substance is released concurrently with the slow redissolution of the crystallized carbohydrate matrix. Nevertheless, as pointed out above, the present claims are not limited by the theory the examiner has proffered. Rather, at paragraph [0083], the present application actually describes the encapsulation method of Schröder as the exact type of encapsulation that the present invention overcomes.

With this in mind, Applicant fails to understand how the examiner can maintain the present rejection over claim 43 and claim 45. Claim 43 recites that none of the insulin is

encapsulated by the porous crystallized dextran microparticles. Claim 45 recites that the insulin is only in the microparticles by being located in pores of the microparticles. On the other hand, Schröder only teaches encapsulation. Schröder only teaches one method for preparing its microparticles – at page 120 – where Schröder teaches emulsification and crystallization to entrap – or encapsulate – the insulin. Claims 43 and 45 expressly exclude encapsulation, and Schröder teaches that its composition is only made by encapsulation. Thus, Applicant submits this alone overcomes the rejection in relation to claims 43 and 45.

Next, the examiner argues that the Schröder composition must read on the present claims because the examiner argues Schröder teaches that insulin is released over time. This is of no effect. The Schröder encapsulated insulin can be released over time because the encapsulating material may remain intact for a certain period of time before being degraded to release the insulin.

At page 15, the examiner expressly states that the microparticles of Schröder have pores by which insulin is released over time. Applicant strongly disagrees with this argument. The examiner is relying upon knowledge of the present invention to read into Schröder disclosure that is not actually present. The examiner must read this document with the eye of the skilled person with no knowledge of the present invention. If this proper perspective is used, it is clear that Schröder does not disclose or suggest the presently claimed invention.

The examiner argues that Schröder discloses pores in the polymer matrix at page 117. Therein, however, Schröder teaches entrapment of proteins in a nonbiodegradable polymer matrix from which the proteins are released by diffusion through pores in the matrix. The examiner's reliance upon this disclosure is improper. This is a disclosure of the prior art from which Schröder teaches away. The actual Schröder composition is not formed of a nonbiodegradable polymer matrix. Moreover, Schröder does not teach that **its** composition of dextran and insulin is porous. Even more important, the present claims exclude entrapment and do not use nonbiodegradable polymer matrices. Thus, the disclosure at page 117 of Schröder is of no effect on the present claims.

The examiner continues to allege that Schröder discloses in Figure 1 that the crystalline polymer matrix has pores. A prior art document must be relied upon for what it teaches, not for the examiner's interpretation of a figure therein. The examiner has pointed to no portion of

Schröder in relation to Figure 1 that teaches that the figure illustrates pores in its dextran microspheres. In the caption, FIG. 1 (a) and FIG. 1(b) are described as being **schematic** views. A skilled person would recognize that a "schematic" is a representation of the elements of a system using abstract, graphic symbols rather than realistic pictures. A schematic usually omits all details that are not relevant to the information the schematic is intended to convey, and may add unrealistic elements that aid comprehension. Nothing in Schröder teaches that the matter schematically illustrated in Figure 1 is a realistic drawing showing pores in the dextran microspheres. Unless the examiner can point to **specific text** in Schröder expressly teaching the presence of pores, it is improper and against prevailing law for the examiner to make an unsupported interpretation of a schematic drawing. The examiner cannot lawfully form a completely unsupported **opinion** as to what a schematic illustrates and then shift the burden to the Applicant to prove otherwise. This is an improper examination tactic. Moreover, the examiner's opinion as to what is schematically illustrated in Figure 1 of Schröder is clear evidence of improper hindsight unless the examiner can point to some teaching in Schröder to support the opinion. Note that the teaching on page 117 of Schröder does not fulfill this burden on the examiner since such teaching relates to the prior art that Schröder expressly teaches away from and expressly teaches that his different composition overcomes. More specifically, the disclosure at page 117 relates to nonbiodegradable polymer matrices, but Figure 1 relates to carbohydrate spheres, which are biodegradable.

At page 14, the examiner argues that if Schröder does not teach release from pores, it is unclear where it would be released from. Again, Applicant respectfully points out that the skilled person viewing Schröder would have knowledge in the art. U.S. Pat. No. 4,713,249 (upon which the examiner also relies) fills this gap in the examiner's understanding. The '249 patent teaches the identical composition as disclosed by Schröder. At column 2 (lines 61-64), the '249 patent teaches that the biologically active substance is released concurrently with the slow redissolution of the crystallized carbohydrate matrix. In other words, the encapsulated insulin is released as the surrounding dextran is dissolved *in vivo*. Nothing in Schröder or the '249 patent teaches release of insulin from pores. It is clear from the art that Schröder teaches release of insulin as the total microsphere redissolves.

Although the present claims recite compositions, not methods of preparing the compositions, Applicant submits that it is proper to consider the method of manufacture as an aid in understanding the differences in the actual compositions. The present claims recite combinations of crystallized dextran microspheres and insulin, wherein the insulin is not encapsulated in the dextran microspheres and wherein the insulin is located in pores of the dextran microspheres. At paragraph [0076], the present specification discloses that a method to manufacture non cross-linked, porous crystallized dextran microparticles includes preparation of a dextran solution, such as an aqueous dextran solution, conducting a crystallization process to form crystallized porous dextran microparticles, and if desired, isolating crystallized porous dextran microparticles from the solution. A therapeutic agent is then permeated into the pores of the microparticles by providing the therapeutic agent into the crystallization solution containing the microparticles or by providing the isolated microparticles and the therapeutic agent into a second solution, such as a second aqueous solution. A specific example is described at paragraph [0048], wherein 3.0 g of Dextran T20 (Pharmacia, Uppsala, Sweden) was dissolved in 2.0 g of water and placed in box at temperature 60 °C. Three hours later, crystallized dextran microparticles were washed by centrifugation at 3,000 g with 3 x 5.0 ml of water. Then the crystallized dextran microparticles were suspended in 2.0 ml of water and allowed to dry at room temperature. The resulting dry powder was used to prepare an insulin containing suspension for the oral insulin delivery experiment. Insulin containing suspensions were prepared by the mixing of 250 mg of the microparticles; 0.3 ml (12 UI) or 0.6 ml (24 UI) of insulin (NovoNordisk Actrapid HM Penfill, 40 UI/ml); and distilled water to reach a volume of 2.0 ml.

This clarifies the actual structure of the presently claimed compositions. Specifically, the compositions are pre-formed crystallized dextran microspheres with insulin permeated into the pores thereof. There can be no encapsulation because the microspheres were preformed. Rather, the insulin takes on a unique type of association with the microspheres by permeating into the pores. This allows for a unique release profile.

By contrast, Schröder teaches a more complex method where dextran and insulin are co-dissolved, and emulsifying medium is added, and a coarse preemulsion is formed. The emulsion is completed by sonication, and this material is poured into acetone to precipitate the microspheres with the insulin encapsulated therein. It is clear that this is a distinct type of

composition from the presently claimed material. The insulin is in a complex relationship with the dextran microspheres in that it is encapsulated within the dextran through intimate admixture with the dextran at the time of crystallization. This is what is illustrated in Figure 1 of Schröder (schematic b) where he shows how the insulin is contained completely within the dextran microspheres and is comingled with further dextran chains within the microsphere.

Accordingly, while the present claims to not recite methods of preparation, this background should clarify how the presently claimed material is different from the Schröder compositions. Applicant respectfully submits that the examiner's view of Schröder has been somewhat tainted by knowledge of the present invention. Applicant submits that if the examiner takes a fresh view of the Schröder disclosure, the examiner will recognize that Schröder only teaches insulin encapsulated in its dextran microspheres and that nothing in Schröder teaches that the insulin is contained in pores of the microspheres. The method of preparation taught by Schröder clearly indicates that permeation into pores is not taking place. Rather, through a complex emulsification and crystallization process, Schröder is encapsulating insulin inside the dextran microspheres. On the contrary, the present claims recite that there the insulin is not encapsulated but is located in pores. These are clear distinctions based on the structure of the composition. The fact that Schröder discloses compositions of dextran and insulin does not mean that the Schröder compositions must be identical to the presently claimed compositions. Rather, Applicant has pointed out clear distinctions in the structure of the claimed compositions versus the compositions taught by Schröder. In light of these distinctions, Applicant submits that the claimed compositions are not anticipated by Schröder, and Applicant respectfully requests reconsideration and withdrawal of the present rejection.

Claims 27-29, 35, 41, 43-45, 47, 49, and 51 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Schröder (U.S. Patent No. 4,713,249). Applicant respectfully traverses these rejections.

Applicant submits that the present rejection is similarly overcome as discussed above in relation to the first Schröder reference. By careful examination, it is clear that the disclosure of the '249 patent is strongly based on the disclosure in the *Biomaterials* journal article.

To reiterate, the examiner makes the argument that since the '249 patent teaches compositions of dextran and insulin, and since the present claims recite compositions of dextran and insulin, they must be identical. This argument is not supported by the art, however, and is actually refuted by the teaching of the '249 patent.

To understand the structure of the microspheres of the '249 patent, the examiner must consider the disclosure therein around the method of making the composition. At column 2 (lines 59-64), the '249 patent teaches that the polymer matrix has such characteristics that it can retain biologically active substances in the non-covalently cross-linked polymeric lattice, the biologically active substance being released concurrently with the slow re-dissolution of the crystallized matrix. In the paragraph bridging columns 3 and 4, the '249 patent describes its complex emulsification process wherein dextran and insulin are co-dissolved, emulsified, and crystallized. This method results in microspheres wherein insulin is **enclosed** (see column 3, lines 60-61, and column 4, line 38, and column 5, lines 10-15, and column 6, line 13, and column 6, line 32, and column 6, line 45, and column 6, line 58, and column 6, lines 65-66, and column 7, lines 5-6, and column 7, lines 13-14, and column 7, lines 20-21, and column 7, lines 36-37, and column 7, line 57, and column 8, lines 12-13). The fact that the insulin is **enclosed** and **is not located in pores** is borne out at column 2 (lines 61-64) – "the biologically active substance being released concurrently with the slow redissolution of the crystallized carbohydrate matrix." Thus, the '249 patent answers the question that the examiner says the office is not equipped to answer, which is how the insulin is released from the Schröder microspheres.

The examiner alleges the burden is on the Applicant to show a novel or non-obvious difference between the claimed product and the product of the prior art. Applicant has met this burden. The composition of the '249 patent has insulin **enclosed** by its microspheres. By enclosing the insulin in the microspheres, the biological activity is retained, and the insulin is released by slow redissolution of the microsphere (i.e., not by release through pores, as the examiner has suggested). On the contrary, the insulin in the presently claimed composition is not encapsulated (or enclosed or entrapped) in the microsphere. Rather, the insulin is located in the pores, which are accessible from outside the microspheres, as illustrated by the method of manufacture, wherein insulin is combined with the dextran only after formation of the

microspheres and permeates into the pores. Thus, Applicant has shown novel and non-obvious differences between the claimed compositions and the disclosure of the '249 patent:

- claimed composition: insulin not encapsulated; insulin located in pores;
- composition of the '249 patent: insulin is encapsulated; insulin not located in pores.

Accordingly, Applicant submits that the claimed compositions are not anticipated by the '249 patent, and Applicant requests reconsideration and withdrawal of the present rejection.

Rejections under 35 U.S.C. §103

Claims 27-29, 32-33, 35, 37, 41, and 43-51 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Schröder (Methods in Enzymology) in view of Moriyama (Journal of Controlled Release, 1996). Claims 27-29, 31, 35-37, 41, and 43-51 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Schröder (Methods in Enzymology) in view of Ecanow (U.S. Patent No. 4,963,526). Claims 27-30, 34, 35, 41, and 43-51 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Schröder (Methods in Enzymology) in view of Clark et al. (U.S. Patent No. 5,783,556). Applicant respectfully traverses these rejections.

As pointed out above, Schröder does not disclose a composition wherein none of the insulin is encapsulated, and Schröder does not disclose a composition wherein the insulin is located in pores of the crystallized dextran microparticles. Since none of the secondary cited references cures this deficiency of Schröder, Applicant submits the present rejections have been improperly applied. Thus, Applicant respectfully requests reconsideration and withdrawal of the present rejections.

Conclusion

Applicant respectfully submits that all claims, as now submitted, are in condition for immediate allowance. Accordingly, a Notice of Allowance is respectfully requested in due course. If any minor formalities need to be addressed, the Examiner is directed to contact the undersigned attorney by telephone to facilitate prosecution of this case.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR §1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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